Form PTO-1390 (REV 10-95) U.S. Department of Commerce Patent and Trademark Office

ATTORNEY'S DOCKET NUMBER: **FMW-XX-PCT-US**

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 10/070583

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/08880	**11 September 2000**	**11 September 1999**

TITLE OF INVENTION: **Device And Method For Leveling Out Titer Plates Used In Screening And/Or Synthesis Systems**

APPLICANT(S) FOR DO/EO/US: **WEBER, Lutz**

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Article 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2))
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3))
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☒ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 10/070583	INTERNATIONAL APPLICATION NO. PCT/EP00/08880	ATTORNEY'S DOCKET NUMBER FMW-XX-PCT-US

17. ☒ The following fees are submitted:

	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492(A)(1)-(5)		
Search Report has been prepared by the EPO or JPO **$890.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) **$710.00**		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$740.00**		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$1,040.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than 20 ☐ 30 ☐ months from the earliest claimed priority date (37 CFR 1.492(e))	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	19-20=	0	X$18.00	$0	
Independent Claims	2-3=	0	X$84.00	$0	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+$270.00	$0	
			TOTAL OF ABOVE CALCULATION =	**$890.00**	
Reduction of ½ for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1,27, 1.28)				$0	
			SUBTOTAL =	**$890.00**	
Processing fee of **$130.00** for furnishing the English translation later than 20 ☐ 30 ☐ months from the earliest claimed priority date (37 CFR 1.492(f)). +				$0	
			TOTAL NATIONAL FEE =	**$890.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				**$.00**	
			TOTAL FEES ENCLOSED =	**$890.00**	
				Amount to be refunded:	$
				Charged:	$

a. ☒ A check in the amount of **$890.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit No. **08-3150**. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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(330) 535-2220

x Daniel J. Hudak Jr.
Signature

Daniel J. Hudak Jr.
Name

47,669
Registration Number

PATENT COOPERATION TREATY
U.S. RECEIVING OFFICE
TO THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Applicant:	**Lutz Weber**
International Application No.:	**PCT/EP00/08880**
International Filing Date:	**11 September 2000**
Title:	**DEVICE AND METHOD FOR LEVELING OUT TITER PLATES USED IN SCREENING AND/OR SYNTHESIS**
Agent's Reference No.:	**FMW-XX-PCT-US**
Date:	**March 8, 2002**

PRELIMINARY AMENDMENT

Sir:

This amendment is based upon the specification and claims as amended in the enclosed Preliminary Examination Report (Amended Pages). Please amend the application as indicated below before calculation of the application fees as follows:

IN THE SPECIFICATION:

Please amend the application as indicated below.

Page 1:

Please replace the first paragraph as follows:

FIELD OF THE INVENTION

The invention concerns a screening and/or synthesis device for performing at least one basic operation, such as adding, releasing, transferring, converting,

detecting, on samples that are contained in reaction vessels of a substance support, especially a titer plate, with at least one receiving device that receives the substance support, as well as a corresponding procedure and the use of such a screening and/or synthesis device.

Page 1:

Please replace the second full paragraph as follows:

BACKGROUND OF THE INVENTION

Such screening and/or synthesis devices are used, for example, in genetic technology and protein chemistry (high throughput screening), molecular biology, combinational chemistry and pharmaceutical active agent research, preferably for the parallel performance of one of the basic operations, such as adding, releasing, transferring, mixing, converting, filtering, evaporating, irradiating; exchanging heat, detecting, in reaction vessels of a substance support, in particular, of a titer plate. The parallel performance of trials also includes a parallel metering of the, by preference, liquid samples, as well as a parallel detection, such as the measurement of fluorescence, and the evaluation of the results of the trial. To this end the familiar titer plates are provided with standardized outer dimensions and a number of, as an example, 96 up to 1,536 reaction vessels. Such titer plates concern wide-area and complex components that are generally manufactured in large numbers at a reasonable cost by injection molding. An overview of screening and/or synthesis systems may be found in the Journal of Bio-molecular Screening, Vol. 3, No. 1, 1998, "Challenges and Opportunities in High Throughput Screening: Implications for New Technologies".

Page 2a:

Please replace the second full paragraph as follows:

SUMMARY OF THE INVENTION

The problem of the invention is therefore to provide a screening and/or synthesis device with a receiving device that receives at least one substance support, in particular, at least one titer plate, and a procedure, so that any manufacturing-induced bending and unevenness of titer plates is leveled out or removed before or while carrying out the basic operation, in particular, before the parallel metering of the reaction vessels and the parallel detection of the results of the reaction, as well as to prevent the aforementioned drawbacks.

Page 13:

Please replace the fourth full paragraph as follows:

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are shown:

Page 14:

Please replace the fifth full paragraph as follows:

DETAILED DESCRIPTION OF THE INVENTION

Fig. 1 shows an ideally level substance support 1 in the form of a segment of 96 reaction vessels 2 of a titer plate 1 with 1,536 reaction vessels 2 and titer plate bottom 3, whereby the reaction vessels 2 are separated from each other by wall areas 4, as well as with a planar basic area 5. In general, titer plates 1 exhibit a titer plate frame 1a and standardized outside dimensions, whereby the reaction vessels 2 with prescribed sample volumes and a modular size are arranged in a matrix arrangement. The titer

plate 1 shown in Fig. 1 comprises a basic area 5 of around 8 x 12 cm., a modular size of 2.25 mm and a sample volume of around 1 μl. Such titer plates 1 are manufactured by injection molding and exhibit manufacturing-induced bending 6 and/or unevenness, since titer plates 1 concern wide-area and complex components, as shown on Fig. 2.

IN THE CLAIMS:

Please substitute the following claims for the pending claim of the same number.

1. (Amended) A screening and/or synthesis device for performing at least one basic operation comprising adding, releasing, transferring, converting or detecting, on samples contained in reaction vessels of a substance support, in particular a titer plate, comprising:
at least one receiving device for receiving the substance support, wherein the receiving device comprises a leveling device that at least partially levels out the substance support before or while or before and while the basic operation is carried out, by subjecting the plate to a pressure force or attraction force, or said pressure force and said attraction force toward a planar area of support.

2. (Amended) A device according to Claim 1, wherein the leveling device comprises a negative pressure device for pressing or attracting, or pressing and attracting the substance support onto the area of support.

3. (Amended) A device according to Claim 2, wherein the negative pressure device comprises at least one vacuum channel connected to the area of support and connected to a negative pressure source.

4. (Amended) A device according to Claim 3, wherein the vacuum channel is arranged in a planar support plate in such a manner that the support plate exhibits multiple suction grooves on a support side turned toward the substance support.

5. (Amended) A device according to Claim 4, wherein the support side of the support plate forms the support surface.

6. (Amended) A device according to Claim 4, wherein a vacuum plate is arranged between the substance support and the support side of the support plate, whereby a top side of the vacuum plate forms the support surface.

7. (Amended) A device according to Claim 6, wherein the vacuum plate exhibits at least one porous layer for the homogeneous attraction of the substance support.

8. (Amended) A device according to Claim 1, wherein the leveling device comprises a pressure plate capable of being subjected to force, for pressing the substance support onto the support surface.

9. (Amended) A device according to Claim 8, wherein the pressure plate is capable of being subjected to mechanical force from above.

10. (Amended) A device according to Claim 8, wherein the pressure plate is capable of being subjected to electro-mechanical force.

11. (Amended) A device according to Claim 8, wherein the pressure plate exhibits multiple pressure pins for pressing the substance support onto the support surface.

12. (Amended) A device according to Claim 11, wherein the pressure pins are distributed on the pressure plate in such a way that they are inserted fully home on wall areas between two reaction vessels of the substance support.

13. (Amended) A device according to Claim 8, wherein the pressure plate exhibits at least one recess in such a manner that the reaction vessels are freely accessible for carrying out at least one of the basic operations.

14. (Amended) A device according to Claim 13, wherein the at least one recesses are designed as holes arranged on the pressure plate in the same modular size as the reaction vessels on the substance support.

15. (Amended) A device according to Claim 4, wherein the support plate or vacuum plate or said support plate and said vacuum plate exhibits a large number of measuring channels for receiving or connecting or receiving and connecting detection elements, which are arranged in the same modular size as the reaction vessels on the substance support.

16. (Amended) A device according to Claim 1, wherein the leveling device is equipped with at least one sensor unit.

17. (Amended) A method comprising: performing in a screening and/or synthesis device at least one basic operation comprising adding, releasing, transferring, converting or detecting, on samples contained in reaction vessels of a substance support, in particular, of a titer plate,

wherein before or while, or before and while the basic operation is carried out the substance support is at least partially leveled out by subjecting the plate to a pressure force or attraction force, or pressure force and attraction.

18. (Amended) A method according to Claim 17, wherein the substance support is leveled out in a screening and/or synthesis device.

19. (Amended) A use of the procedure according to Claim 17 and the screening and/or synthesis device in the search for pharmaceutical active agents, in combinational chemistry and/or biotechnology research and development.

The following is a MARKED version of the amended specification and pending claims with all changes shown in conventional comparison.

IN THE SPECIFICATION:

Please amend the application as indicated below.

Page 1:

Please replace the first paragraph as follows:

FIELD OF THE INVENTION

The invention concerns a screening and/or synthesis device for performing at least one basic operation, such as adding, releasing, transferring, converting, detecting, on samples that are contained in reaction vessels of a substance support, especially a titer plate, with at least one receiving device that receives the substance support, as well as a corresponding procedure and the use of such a screening and/or synthesis device.

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BACKGROUND OF THE INVENTION

Such screening and/or synthesis devices are used, for example, in genetic technology and protein chemistry (high throughput screening), molecular biology, combinational chemistry and pharmaceutical active agent research, preferably for the parallel performance of one of the basic operations, such as adding, releasing, transferring, mixing, converting, filtering, evaporating, irradiating; exchanging heat, detecting, in reaction vessels of a substance support, in particular, of a titer plate. The parallel performance of trials also includes a parallel metering of the, by preference, liquid samples, as well as a

parallel detection, such as the measurement of fluorescence, and the evaluation of the results of the trial. To this end the familiar titer plates are provided with standardized outer dimensions and a number of, as an example, 96 up to 1,536 reaction vessels. Such titer plates concern wide-area and complex components that are generally manufactured in large numbers at a reasonable cost by injection molding. An overview of screening and/or synthesis systems may be found in the Journal of Bio-molecular Screening, Vol. 3, No. 1, 1998, "Challenges and Opportunities in High Throughput Screening: Implications for New Technologies".

Page 2a:

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SUMMARY OF THE INVENTION

The problem of the invention is therefore to provide a screening and/or synthesis device with a receiving device that receives at least one substance support, in particular, at least one titer plate, and a procedure, so that any manufacturing-induced bending and unevenness of titer plates is leveled out or removed before or while carrying out the basic operation, in particular, before the parallel metering of the reaction vessels and the parallel detection of the results of the reaction, as well as to prevent the aforementioned drawbacks.

Page 13:

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BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are shown:

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DETAILED DESCRIPTION OF THE INVENTION

Fig. 1 shows an ideally level substance support 1 in the form of a segment of 96 reaction vessels 2 of a titer plate 1 with 1,536 reaction vessels 2 and titer plate bottom 3, whereby the reaction vessels 2 are separated from each other by wall areas 4, as well as with a planar basic area 5. In general, titer plates 1 exhibit a titer plate frame 1a and standardized outside dimensions, whereby the reaction vessels 2 with prescribed sample volumes and a modular size are arranged in a matrix arrangement. The titer plate 1 shown in Fig. 1 comprises a basic area 5 of around 8 x 12 cm., a modular size of 2.25 mm and a sample volume of around 1 μl. Such titer plates 1 are manufactured by injection molding and exhibit manufacturing-induced bending 6 and/or unevenness, since titer plates 1 concern wide-area and complex components, as shown on Fig. 2.

IN THE CLAIMS:

Please substitute the following claims for the pending claim of the same number.

1. (Amended) A screening and/or synthesis device for performing at least one basic operation[, such as] comprising adding, releasing, transferring, converting [and] or detecting, on samples contained in reaction vessels [(2)] of a substance support [(1)], in particular a titer plate, [with] comprising:
at least one receiving device [(20)] for receiving the substance support [(1)],
[characterized in that] wherein the receiving device [(20)] comprises a leveling device [(21, 21', 21'', 21''', 21'''')] that at least partially

levels out the substance support [(1)] before [and/]or while or before and while the basic operation is carried out, by subjecting [[]the plate[]] to a pressure force [and/]or attraction force, or said pressure force and said attraction force toward a planar area of support [(8)].

2. (Amended) A device [as per] according to Claim 1, [characterized in that] wherein the leveling device [(21, 21')] comprises a negative pressure device [(28, 28')] for pressing [and/]or attracting, or pressing and attracting the substance support [(1)] onto the area of support [(8)].

3. (Amended) A device [as per] according to Claim 2, [characterized in that] wherein the negative pressure device [(28, 28')] comprises at least one vacuum channel [(11)] connected to the area of support [(8)] and connected to a negative pressure source.

4. (Amended) A device [as per] according to Claim 3, [characterized in that] wherein the vacuum channel [(11)] is arranged in a planar support plate [(14,14')] in such a manner that the support plate[(14, 14')] exhibits multiple suction grooves [(22a-c, 22a'-k')] on [the] a support side [(23, 23')] turned toward the substance support [(1)].

5. (Amended) A device [as per] according to Claim 4, [characterized in that] wherein the support side [(23, 23', 23'', 23''')] of the support plate [(14, 14', 14'', 14''')] forms the support surface [(8)].

6. (Amended) A device [as per] according to Claim 4, [characterized in that] wherein a vacuum plate [(9)] is arranged between the substance support [(1)] and the support side [(23)] of the support plate [(14)], whereby [the] a top side [(24)] of the vacuum plate [(9)] forms the support surface [(8)].

7. (Amended) A device [as per] according to Claim 6, [characterized in that] wherein the vacuum plate [(9)] exhibits at least one porous layer [(25a)] for the homogeneous attraction of the substance support [(1)].

8. (Amended) A device [as per] according to Claim 1, [characterized in that] wherein the leveling device [(21'',21''', 21'''')] comprises a pressure plate [(15)] capable of being subjected to force, for pressing the substance support [(1)] onto the support surface [(8)].

9. (Amended) A device [as per] according to Claim 8, [characterized in that] wherein the pressure plate [(15)] is capable of being subjected to mechanical force from above.

10. (Amended) A device [as per] according to Claim 8, [characterized in that] wherein the pressure plate [(15)] is capable of being subjected to electro-mechanical force.

11. (Amended) A device [as per] according to Claim 8, [characterized in that] wherein the pressure plate [(15)] exhibits multiple pressure pins [(19a-c)] for pressing the substance support [(1)] onto the support surface [(8)].

12. (Amended) A device [as per] according to Claim 11, [characterized in that] wherein the pressure pins [(19a-c)] are distributed on the pressure plate [(15)] in such a way that they are inserted fully home on wall areas [(4)] between two reaction vessels [(2)] of the substance support [(1)].

13. (Amended) A device [as per] according to [one of Claims] Claim 8 [through 12], [characterized in that] wherein the pressure plate [(15)] exhibits at least one recess [(30)] in such a manner that the reaction vessels [(2)] are freely accessible for carrying out at least one of the basic operations[indicated in Claim 1].

14. (Amended) A device [as per] according to Claim 13, [characterized in that] wherein the at least one recesses [(30)] are designed as holes [(16)] arranged on the pressure plate [(15)] in the same modular size as the reaction vessels [(2)] on the substance support [(1)].

15. (Amended) A device [as per] according to [one of Claims] Claim 4 [through 7], [characterized in that] wherein the support plate [(14, 14'')] [and/]or vacuum plate [(9)] or said support plate and said vacuum plate exhibits a large number of measuring channels [(13)] for receiving [and/]or connecting or receiving and connecting detection elements, which are arranged in the same modular size as the reaction vessels [(2)] on the substance support [(1)].

16. (Amended) A device [as per] according to [one of Claims] Claim 1 [through 15], [characterized in that] wherein the leveling device [(21, 21', 21'', 21''', 21'''')] is equipped with at least one sensor unit [(37)].

17. (Amended) A method comprising: [in a screening and/or synthesis device for] performing in a screening and/or synthesis device at least one basic operation[, such as] comprising adding, releasing, transferring, converting [and] or detecting, on samples contained in reaction vessels [(2)] of a substance support [(1)], in particular, of a titer plate,

[characterized in that] wherein before [and/]or while, or before and while the basic operation is carried out the substance support [(1)] is at least partially leveled out by subjecting [[]the plate[]] to a pressure force [and/]or attraction force, or pressure force and attraction.

18. (Amended) A method [as per] according to Claim 17, [characterized in that] wherein the substance support [(1)] is leveled out in a screening and/or synthesis device [as per one of Claims 1 through 16].

19. (Amended) A use of the procedure [as per] according to Claim 17 [or 18] and the screening and/or synthesis device [as per one of Claims 1 through 16] in the search for pharmaceutical active agents, in combinational chemistry and/or biotechnology research and development.

Respectfully submitted,

HUDAK & SHUNK CO., L.P.A.

Daniel J. Hudak Jr.

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Attorney Docket No.: FMW-XX-PCT-US (I 861)

DEVICE AND METHOD FOR LEVELING OUT TITER PLATES IN SCREENING AND/OR SYNTHESIS SYSTEMS

The invention concerns a screening and/or synthesis device for performing at least one basic operation, such as adding, releasing, transferring, converting, detecting, on samples that are contained in reaction vessels of a substance support, especially a titer plate, with at least one receiving device that receives the substance support, as well as a corresponding procedure and the use of such a screening and/or synthesis device.

Such screening and/or synthesis devices are used, for example, in genetic technology and protein chemistry (high throughput screening), molecular biology, combinational chemistry and pharmaceutical active agent research, preferably for the parallel performance of one of the basic operations, such as adding, releasing, transferring, mixing, converting, filtering, evaporating, irradiating; exchanging heat, detecting, in reaction vessels of a substance support, in particular, of a titer plate. The parallel performance of trials also includes a parallel metering of the, by preference, liquid samples, as well as a parallel detection, such as the measurement of fluorescence, and the evaluation of the results of the trial. To this end the familiar titer plates are provided with standardized outer dimensions and a number of, as an example, 96 up to 1,536 reaction vessels. Such titer plates concern wide-area and complex components that are generally manufactured in large numbers at a reasonable cost by injection molding. An overview of screening and/or synthesis systems may be found in the Journal of

Bio-molecular Screening, Vol. 3, No. 1, 1998, "Challenges and Opportunities in High Throughput Screening: Implications for New Technologies".

The main problem with manufacturing the titer plates by injection molding is the ensuing bending and/or unevenness of the basic area of the titer plate, whereby the technical expenditure for manufacturing planar titer plates increases with a rising number of reaction vessels. For example, the evenness of the basic area with a titer plate with 96 reaction vessels and dimensions of around 12 x 8 cm^2, in comparison to a level area with a maximum bending value, is typically from 0.5 to 1 mm. Generally the functionality of screening and/or synthesis systems is determined by the unevenness of the titer plates. On the one hand, this limits the metering preciseness of the sample in the reaction vessel, since individual drops of the sample are no longer inserted into the desired reaction vessel. On the other hand, the reliability of the preferred, parallel, optical evaluation of the results of the trial is negatively influenced by this, since varying distances are created due to the bending of the titer plates between the measuring objective and the reaction vessel, which leads to varying positions of the focal points and measuring objective in the parallel detection of the results of the trial in the individual reaction vessels. However, the aforementioned problems may also arise with a temporal sequencing of detection of the reaction vessels and/or the components of individual reaction vessels, with the consequence that undesirable scattering may occur on the walls of the reaction vessels. As a result of the bending of the titer plates used, it may be necessary to calibrate the measuring objective while measuring the titer plates in the z-direction, in order to obtain useable results. This procedure can however only be performed for high throughput procedures at great cost.

An automatic pipette device for micro titer plates is known from Patent Abstracts of Japan, Vol. 009, No. 122 (P-359), May 28, 1985 & JP 60007340A (Denki Kagaku Keiki KK) January 16, 1985, which apparently makes the simultaneous injection of the micro

titer plates possible. To this end a guide plate is provided, which can be moved to the left and right on a base plate. A so-called "pick-up plate" made up of suction elements is arranged above the guide plate. Furthermore, an injection element comprised of injection nozzles is provided. A micro titer plate is mounted on the guide plate. A solution is introduced into the micro titer plate by means of the injection plate and suctioned up via the pick-up plate.

A support plate is known from Patent Abstracts of Japan, Vol. 014, No. 290 (C-0731), June 22, 1990 & JP 02092275 A (Hitachi Ltd.), April 3, 1990, in which cells are fixed by negative pressure, which is set through the filling height of a water tank. The support plate is then brought into contact with the micro titer plate, which picks up the cells.

The problem of the invention is therefore to provide a screening and/or synthesis device with a receiving device that receives at least one substance support, in particular, at least one titer plate, and a procedure, so that any manufacturing-induced bending and unevenness of titer plates is leveled out or removed before or while carrying out the basic operation, in particular, before the parallel metering of the reaction vessels and the parallel detection of the results of the reaction, as well as to prevent the aforementioned drawbacks.

The invention-related solution to this problem, as far as the device is concerned, consists of equipping the screening and/or synthesis device with at least one receiving device with a leveling device at least partially levels out the substance support by subjecting a planar area of support to a pressure force and/or attraction force before and/or while carrying out the basic operation.

subjecting a planar area of support to a pressure force and/or attraction force before and/or while carrying out the basic operation.

The invention-related procedure to be used for this, as per Claim 17 consists of at least partially leveling out the substance support before and/or while carrying out the basic operation, by subjecting [the plate] to a pressure force and/or attraction force on a planar area of support.

By preference, the substance support is leveled out in a screening and/or synthesis device with a leveling device, as per Claims 1 through 16.

The invention-related screening and/or synthesis device and the invention-related procedure are used in the search for pharmaceutical active agents, in combinational chemistry and/or, for example, with bio-technology research and/or syntheses.

By means of the invention-related screening and/or synthesis device with a leveling device, any manufacturing-induced bending and unevenness of wide-area titer plates to be used for, by preference, the parallel performance of trials in screening and/or synthesis devices with multiple reaction vessels, is leveled out or removed over the total basic area of the titer plates. In general, the functionality of highly integrated screening and/or synthesis systems with multiple reaction vessels is improved by the invention, since titer plates with manufacturing-induced bending can be used without any problem. In particular, the reliability of the parallel metering of the samples into the reaction vessels is improved over the entire basic area of the titer plates, since, due to the elimination of the bending and/or unevenness of the titer plates, the relative position of the reaction vessels to each other is defined and the accuracy of the mean of the samples is ensured. Thus, a more precise metering of the sample volume into the reaction vessels is achieved. Furthermore, this causes a clear improvement in the reliability of the parallel, optical reading and/or detection of the results of the trial on the

basic operations performed, since the position of the sample volume and thus the position of the focal points of the measuring objectives to be used in the reaction vessels is unified and/or made parallel in the reaction vessels of the titer plate over the entire basic area of the titer plate. No time-consuming calibration, such as on measuring objectives, is necessary when measuring the titer plates.

The invention-related screening and/or synthesis devices for high throughput comprise a series of workstations. This may include all kinds of workstations familiar to specialists and appropriate as workstations for screening and/or synthesis devices. By preference, this includes such devices as equipment for substance storage, metering stations, measuring stations, transport facilities, facilities for online quality control, facilities for separating substance mixtures, evaluation units, control units, irradiation units, heat exchange units, filter units or evaporation units.

The invention-related screening and/or synthesis devices by preference are equipped with at least one control unit. Preferably, computers are used to guide the steps of the screening and/or synthesis procedure, or rather, coordinate the individual workstations and/or guide the performance of basic operations.

Furthermore, the invention-related devices preferably are equipped with at least one transport device for transporting the substance support among the individual workstations and/or parts of the facilities. This, by preference, concerns plate manipulators for the active positioning of the plates in the workstations, in particular in the form of gripping devices.

The invention-related screening and/or synthesis devices furthermore are, by preference, equipped with at least one substance storage device for substances used in the individual workstations. Substance storage facilities by preference include substance supports or bottles, if necessary, with special equipment to prevent contamination or evaporation.

Furthermore, the invention-related devices preferably include at least one device for separating substance mixtures. The device for separating substance mixtures may involve any device for separating substance mixtures familiar to specialists and capable of high throughput. For example, this includes HPLC, CE and CEC systems. The equipment for separating substance mixtures by preference also includes fraction collectors, which are suitable for receiving small volumes of liquid, such as nano-liter volumes.

In addition, the invention-related devices by preference include at least one metering station. The metering stations include pipette systems and/or dispensing systems, which by preference are controlled piezoelectrically. These systems make access possible to the smallest volumes of liquid, and allow the fast and reproducible addition of components, for example, in nano-liter volumes.

According to the invention, the screening and/or synthesis devices by preference include at least one measuring station. The measuring stations themselves are equipped with at least one detection unit. The detection units contain at least one detection element. The detection units serve to detect characteristics of the samples contained in the reaction vessels of the substance support. All detection units and/or detection procedures familiar to specialists may be used. Preferred detection procedures which may be used in the invention-related device especially include those based on radioactivity, colorimetry, phosphorescence or fluorescence.

Furthermore, for the detection of phosphorescence or fluorescence, the measuring stations by preference contain at least one optical unit for connecting electro-magnetic radiation to the sample and for transferring the radiation emitted from the samples to the detection units. By preference, confocal optics and/or near-field optics are used.

The invention-related device is especially suitable for fluorescence spectroscopy in combination with confocal optics.

The invention-related devices, moreover, are suitable for the use of imaging systems which largely completely map a substance support at a certain time. This especially concerns systems, with which the substance support is laid out on a transparent measuring system plate, such as a planar glass plate, in particular in connection with a tele-centric lens.

Measuring procedures, which, for example, may be used in connection with the invention-related devices, comprise photon distribution analyses, in particular, FIDA and 2-D-FIDA, fluorescence life-cycle analyses, fluorescence polarization analyses, auto and cross correlation analysis of the temporally recorded photons, or combinations thereof.

The invention-related screening and/or synthesis devices are also preferably equipped with at least one evaluation unit. By preference, high-performance computers are used as evaluation units, which control the signal reception and processing.

All stations of the invention-related screening and/or synthesis device by preference are equipped with at least one device for quality control, such as in the form of cameras or sensors. These devices make the online tracking of the screening and/or synthesis processes possible. The monitored parameters run through a feedback and/or improvement process and thus make efficient and reliable processing of the individual working steps possible.

Furthermore, the invention-related screening and/or synthesis device by preference is equipped with at least one filtering system for cleansing the substances or substance mixtures used.

For the irradiation of samples, the devices, moreover, by preference may include at least one radiation unit, in order to irradiate the samples, for example, with biologically active radiation, in particular with UV radiation.

To bring the samples up to temperature the devices contain by preference at least one heat exchange unit.

The individual workstations are designed by preference in such a manner that the screening and/or synthesis device can be operated automatically.

Preferably, all workstations of the screening and/or synthesis devices are equipped with invention-related leveling devices. It is especially preferred that the metering and measuring stations contain at least one leveling device.

The invention-related leveling devices may be an integral component of the receiving device or may be introduced into the receiving device as a module. This particularly makes a retro-fitting of a receiving device with an invention-related leveling device possible. By preference the leveling device is an integral component of the receiving device.

The invention-related leveling devices are by preference equipped with at least one sensor unit. This sensor unit by preference concerns optical, mechanical or electrical sensors, which initiate the leveling procedure after the insertion of the substance support into the leveling device or before or during the performance of the basic operations carried out in the workstations at the time.

Through the invention-related leveling device it is possible to level out the substance support before performing a basic operation. Fortunately, according to this preferred procedure it is no longer necessary to calibrate the optics of the microscopes used

while measuring a substance support because of any unevenness and/or bending.

According to an especially preferred embodiment of the invention, the leveling device comprises a negative pressure device for pressing and/or attracting the substance support onto the area of support. The negative pressure device applies negative pressure on the titer plates included in the receiving device. This causes the tighter plates to be pressed and/or attracted to the planar area of support. By preference, the leveling device of the invention-related screening and/or synthesis device is designed in such a way that in case the substance support is subjected to an attraction force in the form of a vacuum, the substance support is not surrounded by the vacuum as a whole, but instead the vacuum only works on the bottom of the substance support. This favorably prevents the evaporation of sample liquid and thus a possible corruption of measuring results.

According to a particularly favorable, structural embodiment, the negative pressure device exhibits at least one vacuum channel, connected to the area of support, which is connected to a negative pressure source. To this end, the negative pressure device is by preference connected to the negative pressure source by a vacuum support, so that only a vacuum pump is required to evacuate the negative pressure device and thus press and/or attract the titer plate to the planar area of support. In the preferred embodiment, the negative pressure is continued during the performance of the basic operation. It is also conceivable that the negative pressure only continues on the planar area of support until the bending of the titer plate has been eliminated.

According to another especially favorable, structural embodiment, the vacuum channel is arranged in a planar area of support in such a manner that the support plate exhibits multiple suction grooves on the support side turned toward the substance support. Through the preferred arrangement of suction grooves distributed on the areas of support, the titer plate is attracted or pressed with its entire basic area, or rather area-wide, onto the planar area of support. It is also conceivable that vacuum seals can be

integrated into the support side of the support plate, in order to be able to switch off the negative pressure source and nevertheless apply continuous negative pressure to the substance support after closing the negative pressure device by means of a vacuum closure. With this embodiment the support side of the support plate forms the area of support.

According to another preferred embodiment, a vacuum plate is arranged between the substance support and the support side of the support plate, whereby the top side of the vacuum plate forms the area of support. This embodiment as well makes possible an area-wide attraction of the titer plate, since the vacuum plate exhibits at least one porous layer for the homogeneous attraction of the substance support. The porous layer may, for example, consist of sintered metal, plastic or another suitable material. This causes multiple suction openings connected with the layer to arise on the top side of the vacuum plate.

According to another preferred embodiment, the leveling device exhibits a pressure plate capable of being subjected to force, for pressing the substance support onto the area of support. This produces a pressing force directed from the pressure plate in the direction of the titer plates, such that the titer plates are pressed onto the planar area of support.

According to an especially favorable embodiment, the pressure plate is capable of being subjected to mechanical force from above. By preference the pressure plate is capable of being subjected to mechanical force from above, or rather from the side turned away from the titer plate. This, by preference, causes the pressure plate to be pressed from above onto the openings of the reaction vessels of the titer plate, by means of the side turned toward the titer plate, which is leveled out by this.

According to an especially favorable embodiment, the pressure plate may be subjected to electro-magnetic force. With this embodiment, by preference, magnets are arranged in the pressure plate and/or the planar area of support, which produce an electro-magnetic traction to eliminate any bending of the titer plate. For this, by preference,

electro-magnets are also used, since this makes it possible, again to dissolve the traction after eliminating the bending of the titer plate, so as, for example, to transport the titer plate within the screening and/or synthesis device to another receiving device of another workstation for performing one of the aforementioned basic operations, such as, adding, transferring, mixing, converting, filtering, evaporating, irradiating, exchanging heat and detecting.

A special thought of the invention is that only partial areas of the titer plates are subjected to a pressure force and/or attraction force on a planar area of support and are thus leveled. To this end, in a preferred embodiment, the pressure plate exhibits multiple pressure pins for pressing the substance support onto the planar area of support. It is also conceivable that magnets or suction grooves and/or openings are only arranged in local areas in the support plate to this end.

To prevent damage to the reaction vessels of the titer plate, the pressure pins are distributed on the pressure plate in such a manner that they press onto wall areas between two reaction vessels of the substance support.

Another special thought of the invention is to adjust the design of the pressure plate to the requirements of the basic operations to be carried out at the time. In a preferred embodiment, the pressure plate exhibits at least one recess to this end, such that the reaction vessels are freely accessible for performing at least one of the basic operations indicated in Claim 1.

As an especially simple embodiment for the manufacture of the recesses, the recesses are designed as holes on the pressure plate in the same modular size as the reaction vessels on the substance support. Thus, this makes it possible to add or release a preferred liquid sample from above into and/or out of the reaction vessels of the titer plate.

Another special thought on the invention consists of adapting the internal structure of the support plate with a planar area of support and, if necessary, the vacuum plate to the requirements of the basic operations to be carried out at the time. In a preferred embodiment to this end for a measuring station of the screening and/or synthesis device, the support plate and/or vacuum plate exhibits multiple measuring channels to receive and or connect detection elements, which are arranged in the same modular size as the reaction vessels on the substance support. On the one hand, this makes detection, such as an optical fluorescence measurement, possible, by preference in transmission from below through the bottom of the titer plate, whereby the measuring channels are designed in such a way so as not to restrict the optical path. On the other hand, through the use of an aforementioned pressure plate designed as a swage block, the optical measurements can also be made from above through the sample in transmission, whereby optical measuring elements, such as optical detection elements, are arranged in the measuring channels or directly opposite to them, outside the support plate. In a preferred embodiment to this end, the support plate and/or at least the bottom of the support plate consists of a transparent material, such as plastic, glass, or vitreous silica. It is also conceivable that the measuring channels arranged in the support plate are designed in such a manner, such as with a vacuum support, that they are immediately usable as vacuum channels.

The invention-related devices are very appropriate for use in chemical and/or bio-technology research and/or syntheses.

The invention-related devices are very easily applicable for synthesis procedures, in which high throughput is necessary. As an example, they are very easily usable in synthesis procedures based on combinational chemistry. In this manner it is possible to manufacture widely diversified substance banks consisting of a large number of substances within the shortest time in the simplest way. It is customary within the field of combinational chemistry to synthesize substances on the surface of synthetic micro-particles, or rather, polymer spheres.

In particular, the invention-related device can be used for the identification and validation of targets, or rather, specific, biological molecules, such as enzymes, receptors or ion channels, which are possibly significant for certain illnesses or their symptoms, since most active agents influence the biological functioning of a target through their bonding. Furthermore, the device can be used very well for identifying biologically active substances and/or pharmaceutical active agents. Through the capability of the system for high throughput, significantly more substances can be investigated within a short time with regard to their biological activity and/or pharmaceutical effectiveness. This is of particular significance for investigating the substance banks obtained by means of combinational chemistry, with regard to their effectiveness. It is possible with the invention-related device to obtain high throughput and examine from several thousand up to 100,000 substances per day. This has been impossible with the devices known up to now, with the current status of technology.

The invention-related device, moreover, is very suitable for the performance of assay procedures. With these assay procedures, targets and chemical compounds are combined for investigating chemical and/or biological interactive effects. It is thus possible to establish a model system in the easiest way possible, which allows substances to be identified that influence the target in the desired manner. The invention-related device may be used both for biochemical as well as cellular assay procedures. This also includes assay procedures based on the use of vesicular particles or synthetic micro-particles.

The invention-related device is furthermore very suitable for performing assay procedures based on the use of a simplified model systems, which reproduce the physiology in humans or animals. This means that the assay systems may be used, among other things, for obtaining information on the solubility of biologically active and/or pharmaceutically effective substances in blood plasma, their penetration characteristics, liver toxicity, bio-availability, stability in blood or breakdown profile after passing through the liver.

The chemical and biological investigations may, for example, be used i) to identify and characterize biological material or chemical compounds, ii) to identify and/or validate targets, iii) to look for biologically active substances and/or pharmaceutical active agents, iv) to identify master structures, v) for genome analysis, vi) for proteom [misspelled word – likely 'protein'] analysis or vii) to purify and concentrate substrata.

It is the characteristic of the invention-related device that it may be used for high throughput. The invention-related device makes it possible, in comparison to the familiar devices of the current status of technology, to generate a significantly larger volume of data in a given time, thus leading to a significant increase in the effectiveness and reliability of research into active agents.

Other goals, advantages, characteristics and application possibilities of this invention are found in the following description of numerous examples with the use of drawings. For this, all characteristics described and/or pictorially displayed for themselves or in any number of meaningful combinations form the object of the invention, also independent of their summary in the claims or in reference to such claims.

The following drawings are shown:

Figure 1 a) a cross-section and b) a view from above onto a segment of a leveled titer plate with 1,536 reaction vessels,

Figure 2 a cross-section of a titer plate as per Fig. 1 with bending caused during manufacturing,

Figure 3 titer plate as per Fig. 2 in a receiving device of a screening and/or synthesis device with an embodiment of the invention-related leveling device for a metering station,

Figure 4 titer plate as per Fig. 2 in a receiving device of a screening and/or synthesis device with another embodiment of the invention-related device for a measuring station,

Figure 5 A pressure plate for leveling titer plates for a metering station,

Figure 6 A pressure plate for leveling titer plates for a measuring station,

Figure 7 Pressure pins for leveling titer plates for a measuring station.

Fig. 1 shows an ideally level substance support 1 in the form of a segment of 96 reaction vessels 2 of a titer plate 1 with 1,536 reaction vessels 2 and titer plate bottom 3, whereby the reaction vessels 2 are separated from each other by wall areas 4, as well as with a planar basic area 5. In general, titer plates 1 exhibit a titer plate frame 1a and standardized outside dimensions, whereby the reaction vessels 2 with prescribed sample volumes and a modular size are arranged in a matrix arrangement. The titer plate 1 shown in Fig. 1 comprises a basic area 5 of around 8 x 12 cm., a modular size of 2.25 mm and a sample volume of around 1 µl. Such titer plates 1 are manufactured by injection molding and exhibit manufacturing-induced bending 6 and/or unevenness, since titer plates 1 concern wide-area and complex components, as shown on Fig. 2.

The titer plates 1 are used in screening and/or synthesis devices, shown, extremely simplified, in Figures 3 through 7, in various fields of chemical and/or biological research, such as in gene technology and protein chemistry (high throughput screening), molecular biology, combinational chemistry and pharmaceutical active agent research for the parallel performance of various basic operations, such as adding, releasing, transferring, mixing, converting, filtering, evaporating, irradiating, exchanging heat,

detecting, on by preference liquid samples contained in reaction vessels 2. To this end the familiar screening and/or synthesis devices mostly comprise multiple automated workstations arranged in sequence with corresponding receiving devices 20 for the titer plate 1. Typical work stations of a screening and/or synthesis device include a metering station 20a, shown simplified in Figures 3 and 5, with by preference a measuring station 20b, shown simplified in Figures 4, 6 and 7, with by preference a multiple parallel metering system based on a pipette system for monitoring the release and/or addition of liquid into the reaction vessels 2 with, for example, a multiple parallel measuring system based on a CCD camera or a confocal microscope for measuring and evaluating the results of the trial on the basic operations performed.

For the performance of detections, such as optical transmission measurements, through the bottom 3 of the titer plate 1, thinner and more transparent bottoms 3 are necessary, which cannot restrict the optical path. In addition to the bottom thickness, the optical transparence and the bottom roughness, also the levelness of the bottom 3 particularly influences the reproducibility of the optical measurement, since different positions of the focal points of the measuring objectives result in the reaction vessels 2, due to the unevenness and/or bending 6 in the bottom 3 of the titer plate 1, shown in Fig. 2. This can make it necessary, for example, to calibrate the measuring objectives continuously in the z direction during the investigation of various substance supports. As per Fig. 2. a variation 7 in the position of the reaction vessels 2 is provoked over the entire basic area 5 of the titer plate 1 through the unevenness and/or bending 6 in the bottom 3 of the titer plate 1. This causes individual drops no longer to accurately hit the prescribed reaction vessels 2 with multiple, parallel metering systems, so that the most demanding precision of the sample volume is no longer observed. Furthermore, this may cause cross-contaminations in neighboring reaction vessels 2, which corrupts the results of the trial. Therefore, bending 6 and variation 7 of the titer plates 1 is generally reduced to a justifiable degree through costly and separate re-treatment prior to their use in screening and/or synthesis devices.

Nevertheless, in order to be able to use bent titer plates 1 customary to the trade in screening and/or synthesis devices without costly and separate re-treatment, Fig. 3 shows an embodiment of the invention-related leveling device 21 for a receiving device 20 using the example of a schematically represented metering station 20a. Generally, the invention-related leveling device 21 serves to level out titer plate 1 following its reception into the receiving device 20, whereby to this end the titer plate 1, before carrying out the basic operation, such as the release and/or addition of liquid, is leveled out by subjecting [the plate] to a pressure force and/or attraction force on a planar area of support 8.

With the example represented here the leveling device 21 comprises a planar support plate 14 with a support side 23 and a vacuum plate 9 arranged on top of it with top side 24, which forms the planar area of support 8 with this example. First, the titer plate 1 to be leveled out is laid upon the top side 24 of the vacuum plate 9. Then, by means of a negative pressure device 28 integrated into the support plate 14, negative pressure is applied to the top side 24 of the vacuum plate 9, and this causes the titer plate 1 to be attracted and/or pressed onto the planar area of support 8. The negative pressure device 28 comprises a vacuum channel 11 and a vacuum support 12 to this end, which is connected to a negative pressure source, not depicted here.

In order to grasp the titer plate 1 almost evenly the entire basic area 5, thus surface-wise, through the negative pressure, thus attracting the titer plate 1 onto the planar area of support 8, the vacuum channel 11 is arranged in the support plate 14 running in a cross direction and exhibits multiple vacuum branch channels 11a-c pointed vertically toward the titer plate 1. The vacuum branch channels 11a-c come out in the support side 23 of the support plate 14 thus causing numerous suction grooves 22a-c distributed along the support side 23 to appear. For the homogeneous, surface-wise attraction of titer plate 1 the vacuum plate 9, arranged on the support side 23 with the example depicted here, exhibits multiple, porous layers 25a-e, which are made up of openings 26 arranged opposite each other.

This causes a large number of suction openings 27 connected with the layers 25a-e to occur on the top side 24 of the vacuum plate 9.

The titer plate 1 is now attracted along its entire basic area 5 to the planar area of support 8 and/or the top side 24 of the vacuum plate 9 by means of the negative pressure currently applied to the suction openings 27, and is thus level out surface-wise. In doing so, the negative pressure is either maintained during the performance of the basic operations or at least until leveling, and/or a planar titer plate 1 is achieved, as per Fig. 1. As the comparison of both titer plates 1 represented in Figures 1 and 3 shows, an improvement in the function of a metering station 20 of a screening and/or synthesis device is achieved through the leveling out of the titer plate 1, since the bending 6 and the variation 7 of the position of the reaction vessels to is eliminated, as per Fig. 3. This especially guarantees a more precise metering of the sample liquids into the reaction vessels 2, especially with multiple parallel metering systems.

Fig. 4 shows an embodiment of the invention-related screening and/or synthesis device with a leveling device 21' for a receiving device using the example of a schematically represented measuring station 20b. The leveling device 21' comprises a support plate 14' in the form of a measuring system plate 10 with a planar support side 23', which forms the planar area of support 8 with this example. To level out the titer plate 1, the titer plate is directly laid upon the area of support 8 and a negative pressure is produced by means of a negative pressure device 28' now integrated in the measuring system plate 10, as per Fig. 3. This attracts and/or presses the titer plate 1 onto the planar area of support 8 and thus the bending 6 as well as the variation 7 of the position of the reaction vessels 2 is eliminated. The negative pressure is, in turn, maintained while the basic operations are carried out, or at least until a planar titer plate 1 is achieved, as per Fig. 1. It is also conceivable that multiple vacuum seals are arranged in the support side 23', in such a manner that the titer plate 1 is also continuously attracted onto the planar area of support 8 during the performance of the basic area operations, also after closing the vacuum support 12 and switching off the negative pressure device 28'.

In contrast to the support plate 14 in Fig. 3, the measuring system plate 10 in Fig. 4 also exhibits a large number of integrated measuring channels 13. These measuring channels 13 are designed as sack holes with the example represented here and arranged in the same modular size as the reaction vessels 2 of the titer plate 1 between two vacuum branch channels 11a'-k'. Through this arrangement of the measuring channels 13, optic transmission measurements are made possible through an optical path through the bottom 3 of the titer plate 1. To this end, the measuring system plate 10 or at least the bottom 3 of the titer plate 1 is manufactured of transparent material, such as plastic, glass or vitreous silica. Since only the bottom 3 of the titer plate 1 remains under a measuring channel 13 with a low bottom strength in the preferred sub-millimeter area, this also guarantees that the optical path is not restricted.

In another embodiment not represented here the measuring channels 13 are directly connected to the vacuum channel 11 and can therefore be used as vacuum branch channels for attracting the titer plate 1 onto the planar area of support 8.

Fig. 5 shows a further embodiment of the invention-related leveling device 21" for a receiving device using the example of a schematically represented metering station 20a. Before leveling, the titer plates 1 lie on a planar support plate 14" belonging on one of the leveling devices 21" before leveling with planar support side 23", which forms the planar area of support 8 with this example. In contrast to the support plates 14, 14' in Figures 3 and 4, this support plate 14" is not provided with any integrated negative pressure device 28, 28'. The leveling device 21" comprises a pressure plate 15, preferably subjected to mechanical force from above in the arrow-indicated direction 17 for pressing and/or attracting the titer plate 1 onto the planar area of support 8. This force, for example, is produced hydraulically, pneumatically or electromotively and is maintained while the basic operations are performed in the metering station 20a or at least until the bending 6 and the variation 7 of the reaction vessels 2 of titer plate 1 is eliminated, as per Fig. 5. The pressure plate 15 in the example shown here, is of a size

adjusted to the titer plate 1, so as to effect a surface-wide pressing of the titer plate 1 onto the planar area of support 8. To prevent this from damaging the reaction vessels 2 of the titer plate, the titer plate 1, if necessary, is covered with a cover plate prior to pressing.

According to the invention, the force applied to the pressure plate 15 can also be produced magnetically, especially electro-magnetically. So as to make possible here an electro-magnetic traction between the pressure plate 15 and the planar support plate 14", the necessary magnets and/or electro-magnets are arranged in the pressure plate 15 and/or in the planar support plate 14".

One particular thought of the invention is to adjust the current embodiment of pressure plate 15 to the requirements for the current workstation of the screening and/or synthesis device and thus the basic operation to be carried out at the time. As per Fig. 5, the pressure plate 15 for a metering station 20a is designed in the form of a swage block with multiple recesses 30 developed as a hole 16. For this, the recesses 30 are arranged in the same modular size as the reaction vessels 2 on the titer plate 1, so as to make free access to the reaction vessels 2 of the titer plate 1 possible from above and thus the release or addition of liquid.

Fig. 6 shows another embodiment of the invention-related leveling device 21'" with a pressure plate 15 for leveling titer plates 1 for a measuring station 20b. This shows that this pressure plate 15, identical to the embodiment of the pressure plate 15 in Fig. 5, is designed with recesses 30 arranged in the same modular size as the reaction vessels 2 of the titer plate 1 in the form of holes 16. With this example, the recesses 30 make detection possible, such as an optical transmission measurement, from above and below through the liquid samples filled into the reaction vessels 2. For these optical measurements, the support plate 14'" belonging to the leveling device 21'" is designed in the form of a planar measuring system plate 10' without a negative pressure device

28', but with the aforementioned measuring channels 13. The optical elements to be used in the optical measurement, such as CCD detection elements, may either be arranged outside the titer plate 1 and by preference directly below the bottom 36 of the measuring system plate 10', across from the measuring channels 13, or also within the titer plate 1 in the measuring channels 13. To this end the measuring system plate 10' or at least the bottom 36 of the measuring system plate 10' consists of transparent material, such as plastic, glass or vitreous silica. For the performance of the optical measurement, first the titer plate 1 is laid out onto the planar support side 23''' of the measuring system plate 10', as per Fig. 6, whereby this titer plate 1 forms the planar area of support 8. Then, as previously described, the support plate 15 is subjected to hydraulically, pneumatically, electromotively or magnetically created force from above in the arrow-indicated direction 17. This eliminates manufacturing-induced bending 6 and variation 7 in the position of the reaction vessels 2 of titer plate 1, as shown in Fig. 6, and produces a planar titer plate, as per Fig. 1. This causes the position of the reaction vessels to in the titer plate 1 to be exactly defined relative to each other and thus guarantees the reproducibility of the measuring results. Finally, the optical transmission measurement is performed with this planar titer plate 1.

Another particular thought on the invention is that in addition to the leveling of the titer plate 1 through the surface-wide attraction and/or pressing, a point-wise attraction and/or pressing of the titer plate 1 also occurs onto the planar area of support 8. To this end, Fig. 7. shows another preferred embodiment of the invention-related leveling device 21'''' with pressure pins 19a-c for leveling titer plates 1 for a measuring station 20b. For this, individual, or preferably pressure pins 19a-c arranged on a pressure plate 15, not depicted, are subjected to hydraulically, pneumatically, electromotively produced force from above in the arrow-indicated direction 17, for pressing the titer plate 1 onto the planar area of support 8. The pressure pins 19a-c are arranged parallel to each other at such a distance that they press onto the wall areas 4 between two reaction vessels 2 of the titer plate 1 when applying force to the titer plate 1. Through this embodiment, the titer plate 1 is only locally pressed onto these wall areas 4, onto the area of support 8

and is thus leveled in partial areas. Since the pressure pins 19a-c, however, are preferably distributed over the basic area 5 of the titer plate 1, a leveling and/or at least a reduction or balancing of the manufacturing-induced bending 6 and the variation 7 of the position of the reaction vessels 2 is also achieved with this embodiment over the entire basic area 5 of the titer plate 1.

It is also conceivable that magnets are only arranged in local areas of support side 23", 23"' for the point-wise attraction and/or pressing of the titer plate 1 onto the planar area of support 8 in the pressure plates 15, as well as the support plates 14", 14"' shown in Figures 5 and 6. It is also conceivable that to this end the support plates 14, 14' with a negative pressure device 28, 28' shown in Figures 3 and 4 are designed with suction grooves 22a-c only arranged in local areas of the support side 23, 23'.

In general, titer plates 1 with manufacturing-induced bending 6 can be leveled out by the invention. Thus, titer plates 1 manufactured by injection molding can be used without any disadvantages to the functionality, effectiveness and realiability of screening and/or synthesis devices. This also enables the manufacturing requirements for the titer plates 1, and especially the titer plates 1 with a very high number of reaction vessels, such as 1,536 reaction vessels, to be significantly reduced with regard to levelness and bending.

Reference numbers:

1	Titer plate
1a	Titer plate frame
2	Reaction vessel
3	Bottom
4	Wall area
5	Basic area
6	Bending
7	Variation
8	Planar area of support
9	Vacuum plate
10, 10'	Measuring system plate
11	Vacuum channel
11a-c	Vacuum branch channels
11a'-k'	Vacuum branch channels
12	Vacuum supports
13	Optical measuring channel
14-14'''	Planar support plate
15	Pressure plate
16	Hole
17	Direction of force
19a-c	Pressure pin
20	Receiving device
20a	Metering station
20b	Measuring station
21-21''''	Leveling device
22a-c	Suction supports
22a'-k'	Suction supports
23-23'''	Support side
24	Top side
25a-e	Layers
26	Openings
27	Suction openings

28, 28'	Negative pressure device
30	Recesses
36	Bottom
37	Sensor unit

Patent Claims:

1. Screening and/or synthesis device for performing at least one basic operation, such as adding, releasing, transferring, converting and detecting, on samples contained in reaction vessels (2) of a substance support (1), in particular a titer plate, with at least one receiving device (20) for receiving the substance support (1),

   characterized in that

   the receiving device (20) comprises a leveling device (21, 21', 21'', 21''', 21'''') that at least partially levels out the substance support (1) before and/or while the basic operation is carried out, by subjecting [the plate] to a pressure force and/or attraction force toward a planar area of support (8).

2. Device as per Claim 1, characterized in that the leveling device (21, 21') comprises a negative pressure device (28, 28') for pressing and/or attracting the substance support (1) onto the area of support (8).

3. Device as per Claim 2, characterized in that the negative pressure device (28, 28') comprises at least one vacuum channel (11) connected to the area of support (8) and connected to a negative pressure source.

4. Device as per Claim 3, characterized in that the vacuum channel (11) is arranged in a planar support plate (14,14') in such a manner that the support plate (14, 14') exhibits multiple suction grooves (22a-c, 22a'-k') on the support side (23, 23') turned toward the substance support (1).

5. Device as per Claim 4, characterized in that the support side (23, 23', 23'', 23''') of the support plate (14, 14', 14'', 14''') forms the support surface (8).

6. Device as per Claim 4, characterized in that a vacuum plate (9) is arranged between the substance support (1) and the support side (23) of the support plate (14), whereby the top side (24) of the vacuum plate (9) forms the support surface (8).

7. Device as per Claim 6, characterized in that the vacuum plate (9) exhibits at least one porous layer (25a) for the homogeneous attraction of the substance support (1).

8. Device as per Claim 1, characterized in that the leveling device (21'',21''', 21'''') comprises a pressure plate (15) capable of being subjected to force, for pressing the substance support (1) onto the support surface (8).

9. Device as per Claim 8, characterized in that the pressure plate (15) is capable of being subjected to mechanical force from above.

10. Device as per Claim 8, characterized in that the pressure plate (15) is capable of being subjected to electro-mechanical force.

11. Device as per Claim 8, characterized in that the pressure plate (15) exhibits multiple pressure pins (19a-c) for pressing the substance support (1) onto the support surface (8).

12. Device as per Claim 11, characterized in that the pressure pins (19a-c) are distributed on the pressure plate (15) in such a way that they are inserted fully home on wall areas (4) between two reaction vessels (2) of the substance support (1).

13. Device as per one of Claims 8 through 12, characterized in that the pressure plate (15) exhibits at least one recess (30) in such a manner that the reaction vessels (2) are freely accessible for carrying out at least one of the basic operations indicated in Claim 1.

14. Device as per Claim 13, characterized in that the recesses (30) are designed as holes (16) arranged on the pressure plate (15) in the same modular size as the reaction vessels (2) on the substance support (1).

15. Device as per one of Claims 4 through 7, characterized in that the support plate (14, 14") and/or vacuum plate (9) exhibits a large number of measuring channels (13) for receiving and/or connecting detection elements, which are arranged in the same modular size as the reaction vessels (2) on the substance support (1).

16. Device as per one of Claims 1 through 15, characterized in that the leveling device (21, 21', 21", 21"', 21"") is equipped with at least one sensor unit (37).

17. Method in a screening and/or synthesis device for performing at least one basic operation, such as adding, releasing, transferring, converting and detecting, on samples contained in reaction vessels (2) of a substance support (1), in particular, of a titer plate,

characterized in that

before and/or while the basic operation is carried out the substance support (1) is at least partially leveled out by subjecting [the plate] to a pressure force and/or attraction force.

18. Method as per Claim 17, characterized in that the substance support (1) is leveled out in a device as per one of Claims 1 through 16.

19. Use of the procedure as per Claim 17 or 18 and the device as per one of

Claims 1 through 16 in the search for pharmaceutical active agents, in combinational chemistry and/or biotechnology research and development.

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

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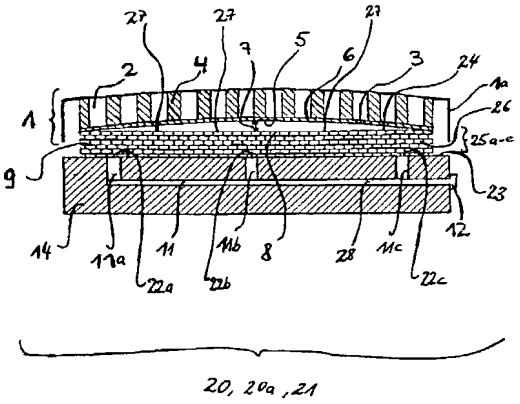
(81) Bestimmungsstaaten *(national)*: JP, US.

[Fortsetzung auf der nachsten Seite]

(54) Title: DEVICE AND METHOD FOR LEVELING OUT TITER PLATES USED IN SCREENING AND/OR SYNTHESIS SYSTEMS

(54) Bezeichnung: VORRICHTUNG UND VERFAHREN ZUR PLANARISIERUNG VON TITERPLATTEN IN SCREENING- UND/ODER SYNTHESESYSTEMEN



(57) Abstract: The invention relates to a screening and/or synthesis device for carrying out at least one basic operation such as adding, releasing, converting, transferring, detecting, on samples that are contained in reaction vessels of a substance support, especially a titer plate, with at least one receiving device that receives the substance support. The invention further relates to a corresponding method. The inventive device is provided with a receiving device that contains a leveling out device that at least partially levels out the substance support before and/or while the basic operation is carried out by subjecting the plate to a pressure and/or attractive force towards a planar area of support. Any bending and/or unevenness that is due to the manufacture of the large-surface titer plate that is preferably used for a simultaneous testing in screening and synthesis systems and that has a multitude of reaction vessels is compensated or removed across the entire base area or at least in partial areas of the titer plate. The inventive device and method improves the functionality, effectiveness and reliability of highly integrated screening and/or synthesis systems since titer plates that are bent due to the manufacture of the plate can be used without problems.

(57) Zusammenfassung: Es wird eine Screening- und/oder Synthese-Vorrichtung zur Durchführung mindestens einer Grundoperation, wie Zugeben, Abgeben, Überführen, Umsetzen, Detektieren, an in Reaktionsgefäßen eines Substanzträgers, insbesondere einer Titerplatte, enthaltenen Proben mit mindestens

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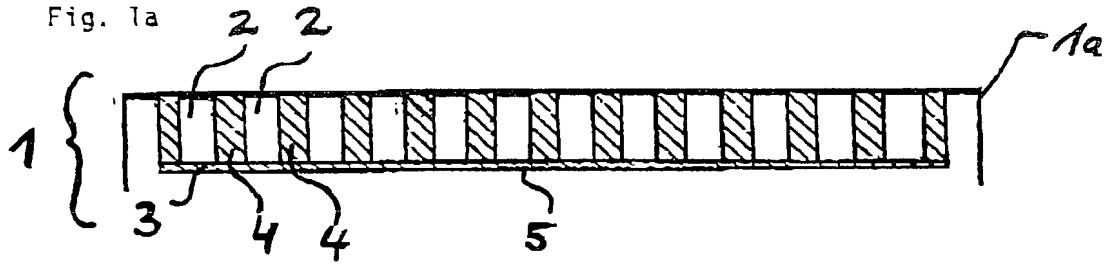
Fig. 1a



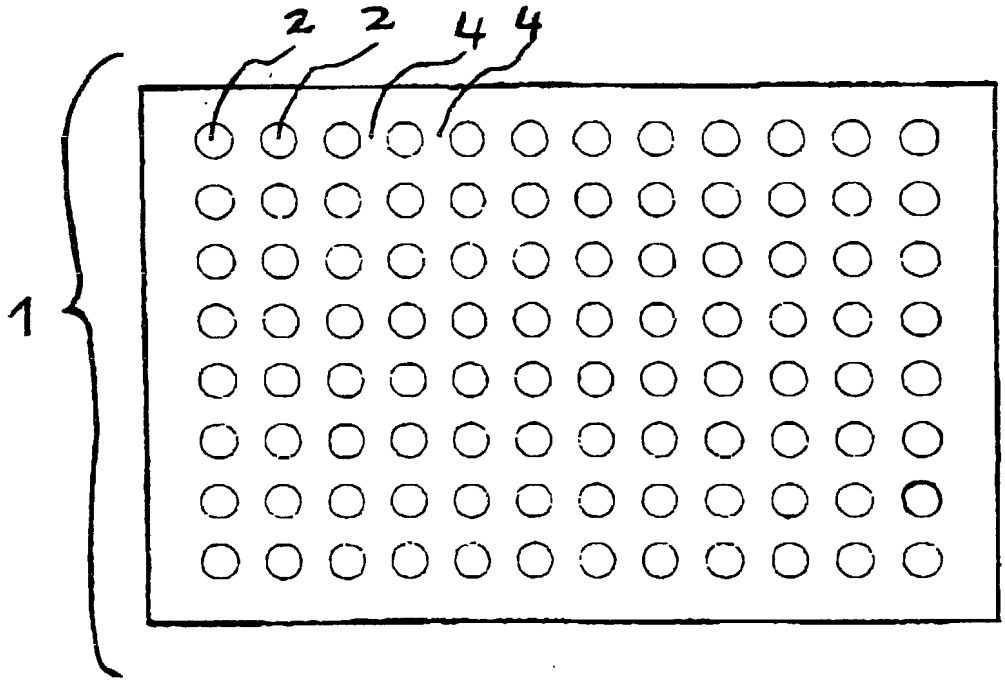


Fig. 1b

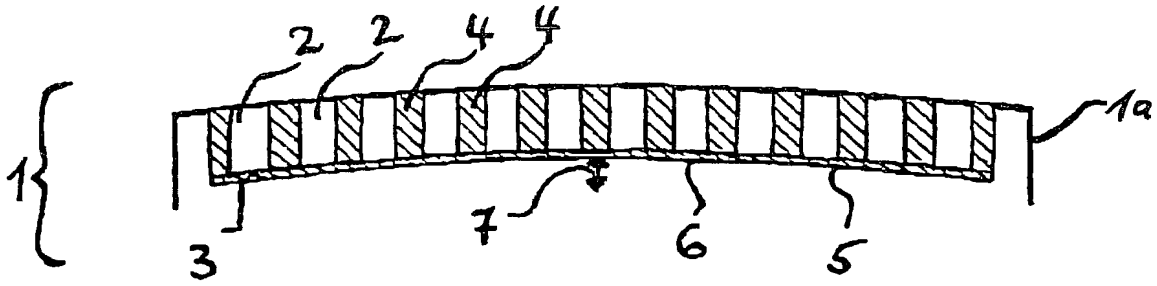


Fig. 2

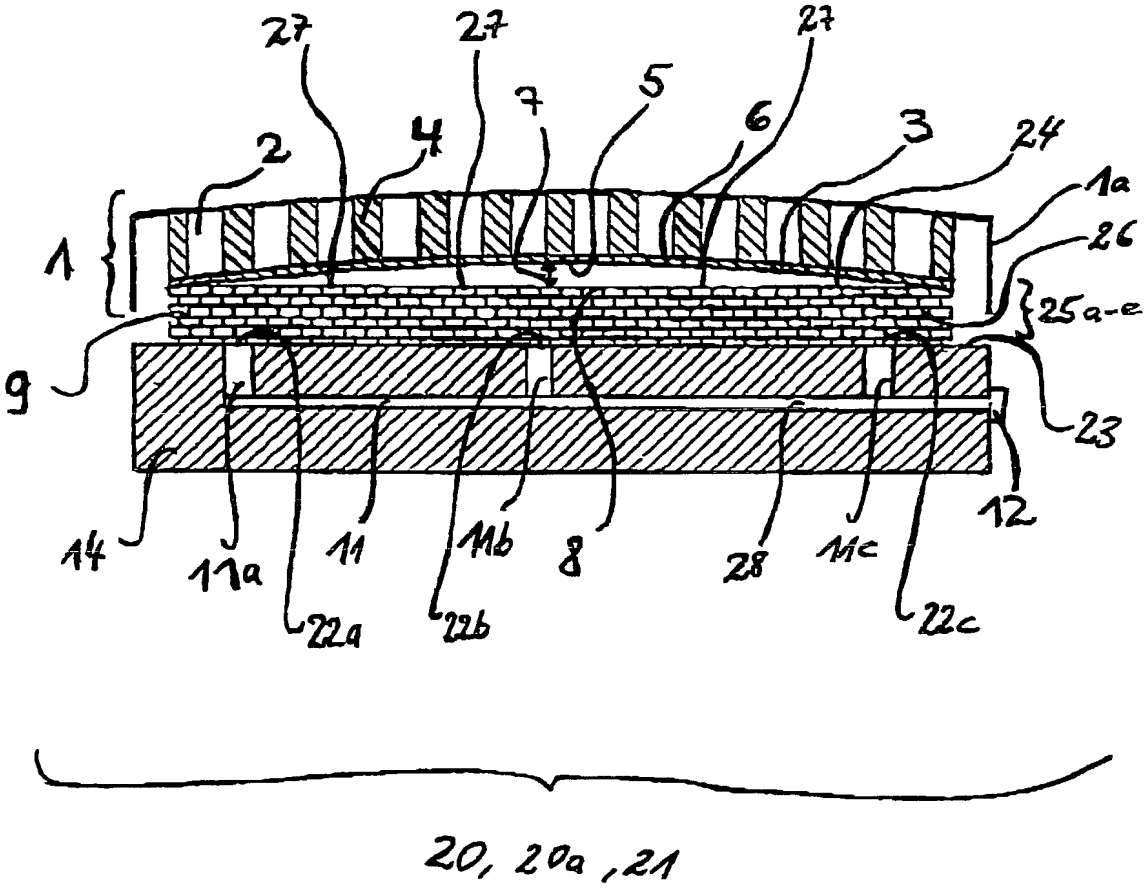

27
27
27
5
7
6
4
2
3
24
1a
1
26
25a-e
9
23
12
14
11a
11
11b
8
28
11c
22a
22b
22c
20, 20a, 21

Fig. 3

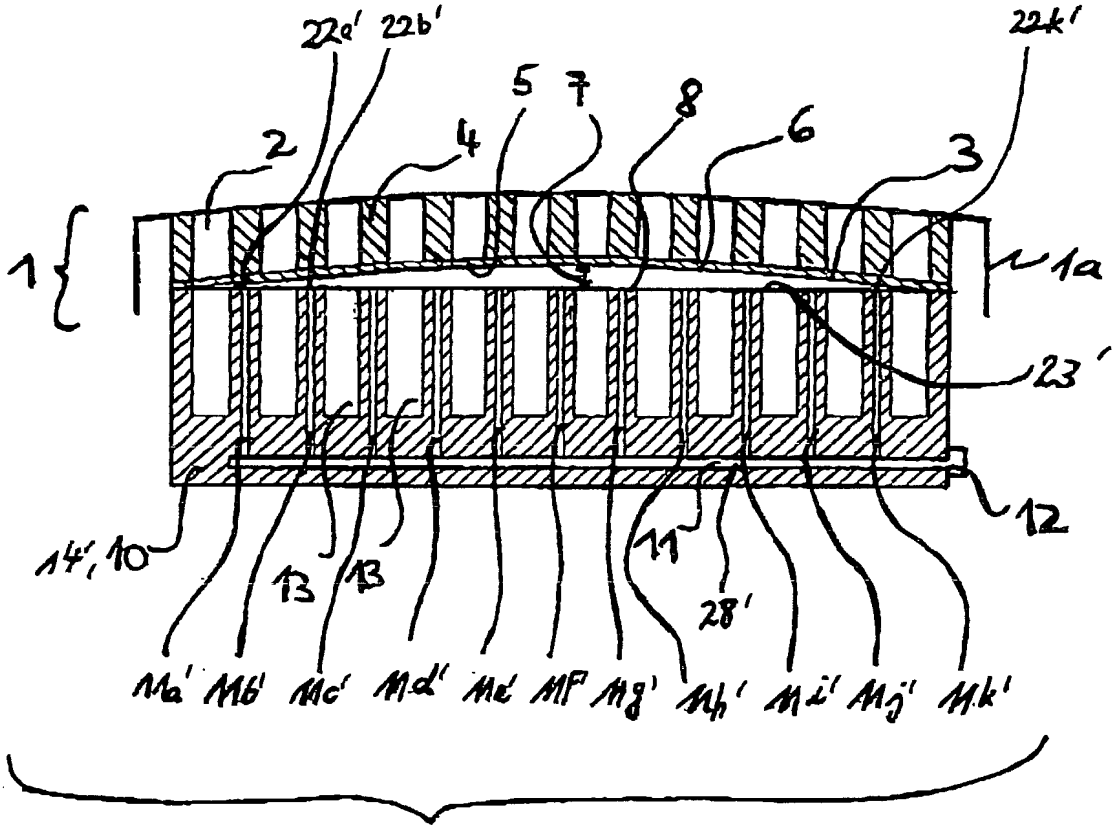

22a' 22b'
22k'
5 7
8
2
4
6
3
1
1a
23'
12
14', 10
13
13
11
28'
Ma' Mb' Mc' Md' Me' Mf' Mg' Mh' Mi' Mj' Mk'
20, 206, 21'

Fig. 4

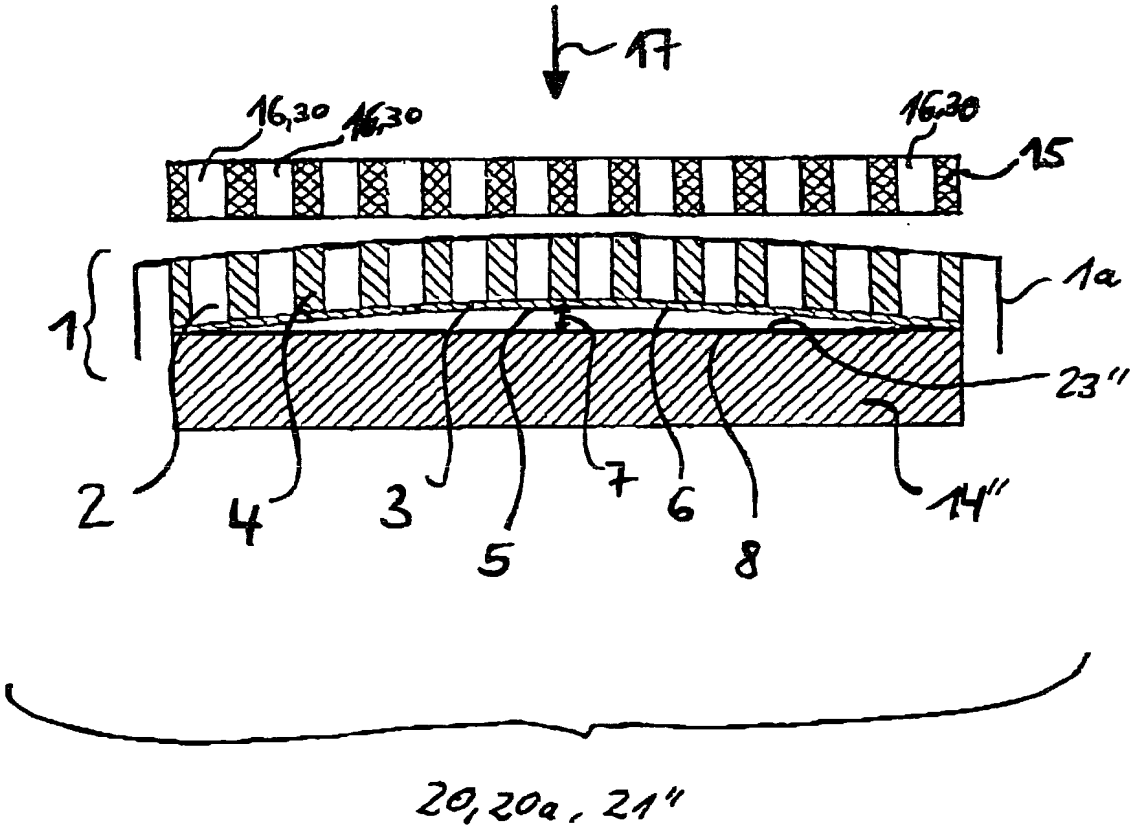


Fig. 5

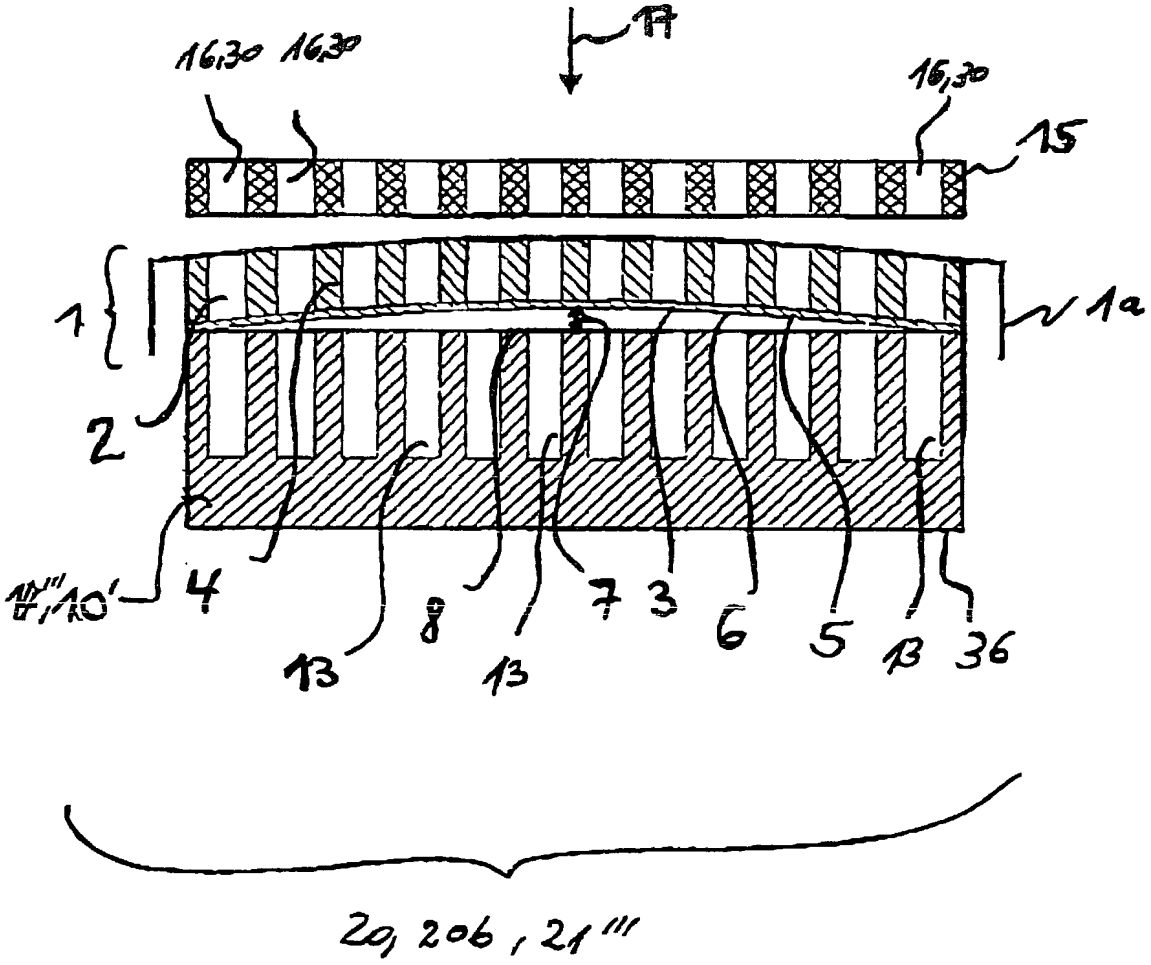


Fig. 6

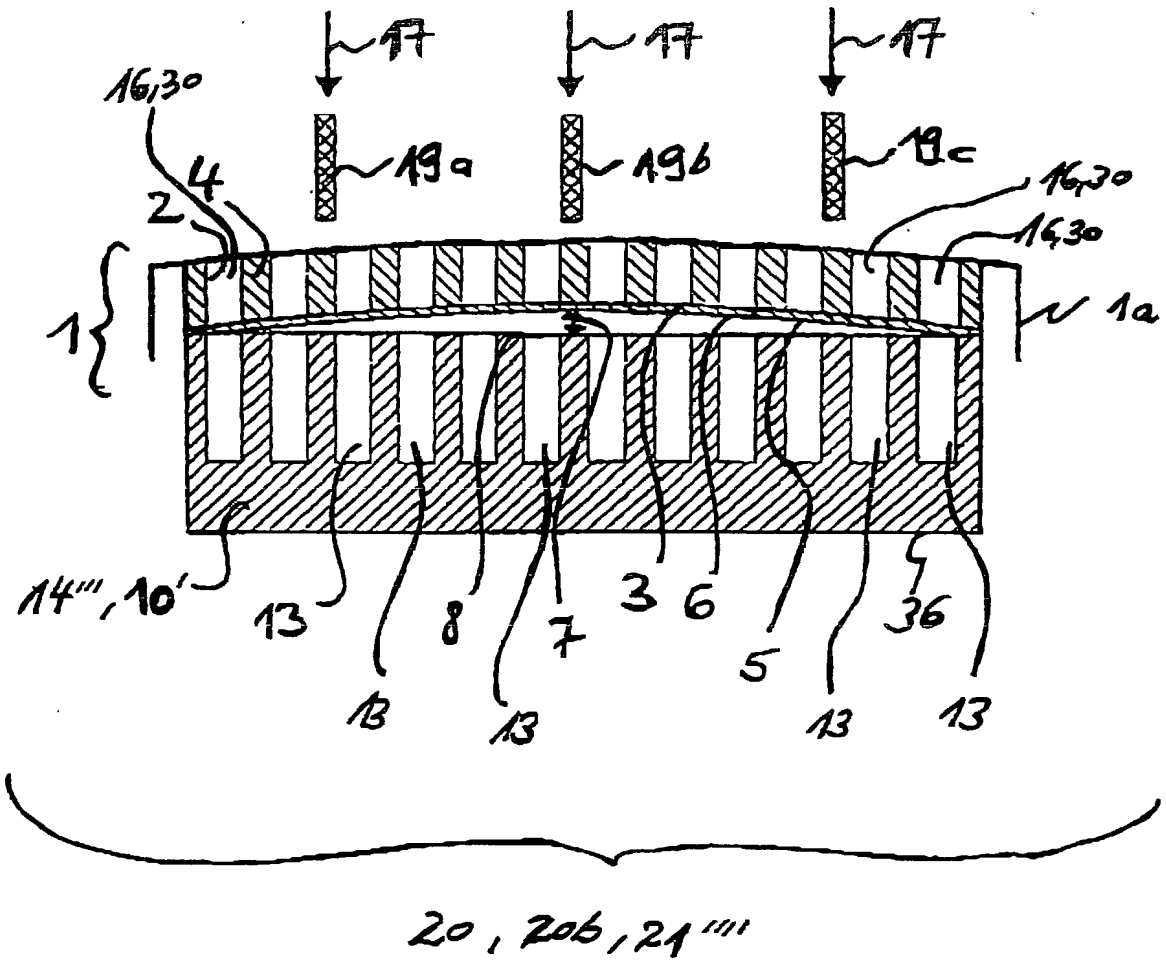

17
17
17
16,30
19a
19b
19c
4
2
16,30
16,30
1
1a
14''', 10'
13
8
7
3
6
5
36
13
13
13
13
20, 20b, 21''''

Fig. 7

PTO/SB/01 (4-96)
Approved for use through 9/30/98 OMB 0651-0032
Type a plus sign (+) inside this box → ☐ Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

☒ Declaration Submitted with Initial Filing OR ☐ Declaration Submitted after Initial Filing

Attorney Docket No.	FMW-XX-PCT-US (I 861)
First Named Inventor	Lutz WEBER
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Group Art Unit	
Examiner Name	

As a below named Inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

"DEVICE AND METHOD FOR LEVELING OUT TITER PLATES USED IN SCREENING AND/OR SYNTHESIS SYSTEMS"

(Title of the Invention)

the specification of which

☐ is attached hereto
OR

☒ was filed on (MM/DD/YYYY) 09/11/2000 as United States Application Number or PCT International

Application Number PCT/EP00/08880 and was amended on (MM/DD/YYYY) 10/06/2001 (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? Yes	No
199 43 443.3	DE	09/11/1999		☐	☒
				☐	☐
				☐	☐
				☐	☐
				☐	☐
				☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	
		☐ Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

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(July 1996)

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DECLARATION

Page 2

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*
	PCT/EP00/08880	09/11/2000	

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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SHUNK, Laura F.	31,423	HUDAK, Daniel J. Jr.	47,669
ROTE, Frank C. Jr.	20,395	FARINE, Cheryl L.	36,796
SHUST, Nestor, W.	23,034		

(17)

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

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☐ Additional inventors are being named on supplemental sheet(s) attached hereto.